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Vast applications of botulinum neurotoxin in neurology - systematic review

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Abstract

Introduction and aim: Botulinum neurotoxin (BoNT), a protein naturally produced by bacteria from the Clostridium family, has evolved into a cornerstone therapy in neurology. The aim of this article is to examine the clinical applications, safety profiles and emerging applications of BoTN in neurology.

Review methods: This review is based on publicly avalible PubMed, MDPI and Google Scholar databases, targeting studies published between January 2019 and March 2025. Search terms included “botulinum toxin in neurology”, “BoNT-A in spasticity,” “chronic migraine,” “neuropathic pain treatment” “dystonia treatment”, “hemifacial spasm treatment” and “BoNT-A/B”.

Brief description of the state of the art: Through its mechanism of action—blocking acetylcholine release by cleaving SNARE proteins—BoNT enables localized and reversible neuromuscular blockade. Upon oral ingestion, BoNT causes the neuroparalytic syndrome botulism, but BoNT injections are used to manage chronic medical conditions across multiple indications. Since its first therapeutic use in the 1980s, BoNT has been widely adopted for medical and cosmetic applications. In addition to its established role in treating hyperkinetic movement disorders such as dystonia and spasticity, BoNT has demonstrated significant effectiveness in managing a range of autonomic nervous system disorders. Especially serotyoes A and B are utilized, showing both safety and efficacy.

Summary: Applications of botulinum toxin have demonstrated continued growth in therapeutic scope, reinforcing its value across neurology. With the accumulation of clinical evidence and technological advancements, BoNT's role is constantly expanding and offering targeted relief with minimal systemic effects.

Keywords: botulinum toxin, spasticity, dystonia, chronic migraine, neuropathic pain, hemifacial spasm

1. Introduction

Botulinum toxin (BoNT) is a potent neurotoxin produced by the anaerobic bacterium Clostridium botulinum, and is recognized as one of the most powerful biological substances known. The toxin exists in seven immunologically distinct serotypes (A–G), with serotypes A and B being the most extensively studied and utilized in clinical practice due to their favorable therapeutic profiles and duration of action [1].

BoNT exerts its effect by cleaving specific proteins involved in the release of acetylcholine from presynaptic nerve terminals. This results in a reversible inhibition of synaptic transmission at both the neuromuscular junction and autonomic cholinergic synapses. Specifically, BoNT-A targets SNAP-25, a component of the SNARE complex, thereby preventing vesicular fusion and subsequent neurotransmitter release. The inhibition is temporary and localized, as axonal sprouting and regeneration of synaptic function typically restore neurotransmission within several months [2].

Historically, BoNT was primarily associated with the clinical manifestations of botulism, a severe neuroparalytic illness. However, since its first therapeutic use in the 1980s, BoNT has been widely adopted for medical and cosmetic applications. In addition to its established role in treating hyperkinetic movement disorders such as dystonia and spasticity, BoNT has demonstrated significant efficacy in managing a range of autonomic nervous system disorders. Additionally, its use in other disorders, such as chronic migraine, is still being researched [3].

The increasing scope of BoNT's therapeutic applications can be attributed to its dual capacity to modulate both somatic and autonomic nerve activity with a high degree of precision and minimal systemic adverse effects. Its localized action, long duration of effect, and reversibility render it an attractive option for conditions in which conventional pharmacologic therapies are either insufficient or associated with intolerable side effects.

Thus, botulinum toxin represents an example of how a naturally occurring toxin can be purposed into a versatile pharmacologic tool in neurology.

2. Methods

This review is based on publicly available PubMed, MDPI and Google Scholar databases, targeting studies published between January 2019 and March 2025. Search terms included "botulinum toxin,", "spasticity," "chronic migraine," "neuropathic pain," "dystonia,", "hemifacial spasm" and "BoNT-A/B".

3. Clinical Applications

3.1. Spasticity is a common complication associated with numerous neurological disorders involving upper motor neuron lesions, such as stroke, multiple sclerosis (MS), and cerebral palsy. Managing this challenging condition remains a leading focus of research involving botulinum toxin.

An analysis of recent studies show that BoNT-A injections remain invaluable in spasticity treatment across various neurological disorders [4]. Key points raised by the authors in recent works include:

- Botulinum toxin type A (BoNT-A) has demonstrated substantial efficacy in reducing muscle tone, particularly in both the upper and lower limbs, making it a valuable intervention for managing spasticity in various neurological conditions [5].
- BoNT-A injections are effective long-term, especially when they are integrated into a comprehensive rehabilitation program. In particular, multimodal strategies that incorporate task-specific therapies have been shown to amplify and sustain the therapeutic effects, offering significant improvements in functional performance and pain reduction. Moreover, these positive outcomes appear to be consistent regardless of patient age, spasticity severity, or prior treatment history [6,7].
- BoNT-A has been well-tolerated even at higher doses (≥600 units), though standardized dosing protocols should be established to ensure consistent clinical application and optimal therapeutic outcomes [5,8].
- Comparative studies have highlighted the superior durability of BoNT-A's therapeutic effect relative to alternative modalities, such as extracorporeal shock wave therapy, reinforcing its value as a primary intervention[9].

- BoNT-A shows strong cost-effectiveness, particularly when administered early following acute neurological events. This early intervention approach has been associated with long-term reductions in healthcare burden and improved quality-adjusted life years (QALYs), underscoring its potential to deliver both clinical and economic value [5,10].
- In disease-specific applications, BoNT-A has demonstrated notable efficacy in patients with multiple sclerosis (MS), with reductions in spasticity (as measured by the Modified Ashworth Scale) sustained for up to 12 weeks post-injection (Systematic Review, 2024 – Medical Journal of Rehabilitation and Health). Similarly, in cerebral palsy management, BoNT-A has proven effective, especially when combined with targeted rehabilitation strategies. These findings emphasize the necessity for individualized dosing and tailored treatment plans to maximize therapeutic outcomes [11,12].

3.2. Dystonia is a neurological movement disorder characterized by involuntary muscle contractions, leading to repetitive movements or abnormal postures [13]. Botulinum toxin injections are used to treat a large number of muscle hyperactivity syndromes. Use in dystonia is still one of the most important indications for BoNT therapy and remains first-line therapy in treatment of this complication [14].

Analyzing recent articles provides useful insights into the use of BoNT for treating various forms of dystonia with few important points listed as:

- BoNT remains a gold standard for effective treatment of various focal dystonias such as cervical dystonia (neck muscle spasms), blepharospasm (eyelid twitching), laryngeal dystonia (voice disturbances), with significant improvement in motor function and pain reduction in most patients [14]
- The therapeutic effects of BoNT typically last about 3–4 months, and regular reinjections are necessary to maintain symptom relief, though intervals should remain flexible and adjusted to keep patients symptom-free [15].
- Long-term studies, some spanning over 25 years, show that BoNT remains both safe and effective for patients with adult-onset cervical dystonia [13].
- BoNT treatment is often more effective when combined with other treatments, such as deep brain stimulation and intrathecal baclofen, to enhance positive clinical outcomes [16].

- Integrating physical therapy alongside BoNT injections has also been shown to improve outcomes, especially in cervical dystonia, by enhancing muscle control and reducing compensatory movements [17].
- While rare, some patients may develop immunoresistance to BoNT, potentially reducing its efficacy over time. Switching between BoNT serotypes can help manage this issue[17].

3.3. Chronic migraine (CM) is a debilitating neurological disorder characterized by headaches occurring on 15 or more days per month for at least three consecutive months, with features of migraine on at least eight of those days. It affects approximately 1–2% of the global population and poses a significant burden on individuals' quality of life, productivity, and mental health. CM often evolves from episodic migraine and is associated with risk factors such as medication overuse, high stress levels, and conditions like depression and anxiety [19]. Due to its complex nature and resistance to many conventional therapies, CM requires a multidisciplinary and individualized treatment approach.

An analysis of recent articles provided following insights into the use of BoNT for CM treatment:

- Clinical trials have demonstrated that BoNT-A significantly reduces the number of headache days per month in individuals with CM. For example, the PREEMPT trials reported a reduction of approximately 9 headache days per month compared to baseline [18].
- BoTN-A’s exact mechanism of action in managing CM is still being investigated. It is believed to inhibit the release of neurotransmitters and inflammatory mediators involved in pain pathways, such as calcitonin gene-related peptide (CGRP). These actions reduce peripheral sensitization and may indirectly diminish central sensitization within the trigeminovascular system [19].
- Longitudinal studies, such as the COMPEL study, indicate that sustained BoNT-A therapy over two years still leads to ongoing reductions in headache frequency and improvements in quality of life. This supports its role as a long-term management option for CM [19,20].
- Although some patients experience benefits after the first cycle, optimal results often require at least two or more treatment cycles over the course of 6–12 months. This delay in effect may be frustrating for patients seeking rapid relief, especially compared to certain oral preventives [18].

- Evidence suggests a potential dose-response effect, with increased efficacy observed in patients receiving 195 units versus the standard 155 units. Patients reported further reductions in headache frequency and intensity with higher dosing [21].
- BoNT-A has been found to be more effective than some compared treatments, such as oral preventive medications (e.g.topiramate) in achieving a ≥50% reduction in headache frequency among CM patients [20].
- BoNT-A is generally well tolerated, with side effects such as neck pain and localized muscle weakness being the most commonly reported. These are usually mild and might be attributed to the injection process itself. No significant drug interactions have been documented, and the safety profile is maintained even over long-term use [20].
- Not all patients respond to BoNT-A treatment. Approximately 30–40% are considered non-responders, even after several injection cycles. Factors influencing poor response may include variations in migraine pathophysiology or suboptimal injection technique. Additionally, BoNT-A tends to be more effective in patients without aura and appears to have limited benefit in managing aura-related symptoms [20].

3.4. Neuropathic pain (NP) is a type of pain that results from damage or disease affecting the somatosensory nervous system. It can originate from pathological changes in both the peripheral nervous system and the central nervous system (CNS). Contributing factors include viral infections such as herpes simplex, varicella zoster, and HIV; metabolic disorders involving mitochondrial dysfunction, such as diabetes; stroke; mechanical injuries to the CNS or peripheral nerves; and exposure to toxic agents, particularly chemotherapeutic drugs like oxaliplatin and vincristine. NP encompasses several common neurological pain syndromes, including trigeminal neuralgia (TN), postherpetic neuralgia (PHN), diabetic neuropathic pain (DN), and postsurgical neuralgia [22].

Recent research has examined the use of botulinum toxin (BoNT), particularly type A (BoNT-A), as a therapeutic option for NP. The key points from these studies might be summarized as below:

- BoNT-A injections have shown effectiveness in alleviating neuropathic pain associated with various conditions such as trigeminal neuralgia, diabetic neuropathy, postherpetic neuralgia, and spinal cord injury-related pain. Patients frequently reported significant pain relief, often lasting several months [22,23].
- The analgesic effects of BoNT-A are thought to result not only from inhibition of acetylcholine (ACh) release at neuromuscular junctions, but also from its ability to

modulate the release of pain-related neuropeptides such as substance P, glutamate, and calcitonin gene-related peptide. Additionally, BoNT-A may help reduce neurogenic inflammation and influence ion channels involved in pain signal transmission [23].

- In the reviewed studies, BoNT-A was typically employed as a second-line treatment in patients who had not responded to prior pharmacological therapies [22].
- According to researchers BoNT-A injections are generally safe for treating neuropathic pain, with minimal notable side effects. Patients tolerate the treatment well, and adverse events are reported infrequently[24].
- Formulations, dosages, injection techniques, and targeted muscles vary across studies, making it challenging to establish standardized BoNT-A treatment protocols. Further research is required to refine optimal dosing, administration protocols, and to assess the long-term effects[22].
- BoNT-A treatment shows limited efficacy in certain cases, not providing significant pain relief. For instance, one report highlighted two cases of trauma-induced neuropathic pain where BoNT-A injections did not yield the desired analgesic effects, suggesting that its efficiency may vary depending on the cause of neuropathic pain [25].

3.5 Hemifacial spasm (HFS) is a chronic neurological disorder characterized by involuntary, intermittent contractions of the muscles innervated by the facial nerve (cranial nerve VII) on one side of the face. These spasms typically begin around the eye and may progressively involve other facial muscles, including the cheek, mouth, and neck regions. HFS is most commonly caused by neurovascular compression at the root exit zone of the facial nerve, although it can also occur secondary to facial nerve injury or idiopathically [26,27].

While not life-threatening, HFS can significantly impair quality of life by causing facial discomfort and social embarrassment. The condition is typically progressive if left untreated. First-line treatment options include botulinum toxin (BoNT) injections and for patients with severe or refractory symptoms, surgical microvascular decompression (MVD) may be considered as a more definitive intervention [27,28].

Analyzing recent articles provides following useful insights into the use of BoNT for treating HFS:

- BoNT is consistently highly-effective in reducing both the frequency and severity of facial spasms in HFS. Meta-analyses report improvement in 73–98.4% of patients. Patients typically observe symptom relief within a few days following injection, with peak therapeutic effects occurring within one to two weeks. BoNT injections are particularly beneficial for patients who do not qualify for MVD due to factors such as advanced age, comorbid medical conditions, or uncertain diagnosis [26,27].
- The duration of BoNT's therapeutic effect generally ranges 12-15 weeks, necessitating re-injection as the clinical benefit diminishes. The exact duration can vary depending on individual patient response and the specific BoNT formulation utilized [27].
- Adverse effects are usually mild, transient, and localized. The most commonly reported include: transient facial weakness (due to diffusion of toxin to nearby muscles),ptosis and mild asymmetry in facial expression. These side effects are reversible and typically resolve as the pharmacologic activity of BoNT subsides [26,28].
- Injection precision is essential to maximize therapeutic outcomes and minimize complications. Proper anatomical localization ensures targeted delivery and reduces the likelihood of unintended diffusion. Typically targeted muscles include: orbicularis oculi, zygomaticus, orbicularis oris, and depressor anguli oris [28].
- Dosages vary and depend on several factors, including muscle size, severity of symptoms, and individual response. Over time, dose adjustments may be required to sustain benefits or to mitigate side effects. Longitudinal studies suggest that BoNT remains effective over years of repeated administration, with no significant development of resistance or reduction in therapeutic response, provided that optimal dosing and injection intervals are maintained [27,28].
- Optimal clinical outcomes are achieved when treatments are tailored to each patient's symptoms, including specific muscle involvement, symptom progression and prior response to injections. Furthermore, personalized intervals between sessions (usually 3–4 months) help maintain consistent symptom relief [26,28].
- Although BoNT is not a curative intervention, it provides substantial symptomatic relief and represents an important non-surgical option for patients either delaying or avoiding operative intervention, or those whose symptoms are not severe enough to warrant invasive treatment [27].

3.6 Autonomic nervous system (ANS) disorders. Botulinum toxin has emerged as a clinically valuable therapeutic agent for the management of various autonomic nervous system (ANS) disorders, particularly those associated with Parkinson's disease (PD) and other forms of dysautonomia [29]. An analysis of recent research highlights its efficacy in treating conditions such as sialorrhea, hyperhidrosis, overactive bladder (OAB):

- Sialorrhea is a prevalent non-motor symptom in PD and other neurological disorders. It significantly impairs quality of life and increases the risk of aspiration. BoNT injections administered into the parotid and submandibular glands have been shown to effectively reduce salivary flow, thereby alleviating drooling, reducing respiratory complications and enhancing social functioning. Furthermore, this intervention is generally well-tolerated, with minimal adverse effects such as dry mouth or mild dysphagia [29]
- Hyperhidrosis can present as a primary idiopathic condition or be secondary to neurological diseases. BoNT is approved by the FDA for the treatment of axillary hyperhidrosis and is also used off-label for palmar, plantar, and facial sweating. Clinical use has demonstrated that BoNT injections provide symptomatic relief for an average duration of 4 to 9 months, necessitating repeat treatments for sustained effect. This therapy is particularly beneficial for patients who do not respond adequately to topical or systemic anticholinergic medications [29,30].
- Overactive Bladder (OAB) and urinary incontinence are common autonomic complications in patients with neurogenic bladder (e.g. resulting from multiple sclerosis or spinal cord injury). Intradetrusor injections of BoNT reduce involuntary bladder contractions, leading to improved bladder capacity, fewer urgency episodes, and decreased incontinence. While effective, treatment must be repeated approximately every 6 to 9 months. A notable adverse effect is the risk of urinary retention, which may necessitate intermittent catheterization [30].
- BoNT is generally well-tolerated when administered by trained clinicians, with proper anatomical targeting and patient selection crucial for minimizing risks. Most adverse effects are localized and dose-dependent, including temporary muscle weakness or dry mouth. Due to its localized mechanism of action, systemic side effects are rare [29,30].
- BoNT provides targeted symptomatic relief but does not modify disease progression. Its therapeutic role continues to expand, with a growing body of evidence supporting its use across a spectrum of autonomic disorders, particularly those of neurological

origin. However, several areas require further investigation, including optimal dosing regimens for different autonomic targets, long-term safety and efficacy profiles, and the potential application of BoNT in gastrointestinal and cardiovascular autonomic dysfunction. Randomized controlled trials remain limited in many of these areas, especially beyond PD and bladder dysfunction[29,30].

3.7. **Essential Tremor (ET)** is a common neurological movement disorder characterized by involuntary, rhythmic shaking, most often affecting the hands, but it can also involve the head, voice, and other body parts. It typically worsens with movement (action tremor) and can impact daily activities. **Head Tremor** in the context of essential tremor refers to an involuntary, rhythmic movement of the head—usually in a "yes-yes" (vertical) or "no-no" (horizontal) pattern [31].

An analysis on recent data presents following points about usage of BoTN in ET's treatment:

- Botulinum toxin has shown moderate and clinically meaningful efficacy in reducing the severity of essential head tremor, particularly in patients who do not respond to oral medications. While the treatment does not eliminate tremor entirely, it can lead to significant functional improvement and symptom relief in a substantial subset of patients. Its effects are temporary, requiring repeated injections every few months, and outcomes are highly dependent on precise muscle targeting. Overall, BoNT is a valuable therapeutic option, especially when carefully administered by experienced clinicians [32,33].
- Patients receiving BoNT injections reported side effects such as neck pain, posterior cervical weakness, and dysphagia. These effects were generally mild to moderate and transient. BoNT carries a boxed warning regarding the potential spread of toxin effects beyond the injection site, which can lead to serious symptoms like difficulty swallowing or breathing. While rare, these risks necessitate careful patient selection and monitoring [34].
- While BoNT is FDA-approved for several conditions, its use in treating EHT is off-label. The American Academy of Neurology acknowledges BoNT as a treatment option for EHT, particularly in cases where patients do not respond to first-line oral therapies [34].
  https://www.medicalnewstoday.com/articles/drugs-botox-for-essential-tremor

- Electromyography (EMG) and ultrasound guidance are employed to enhance the precision of BoNT injections, aiming to maximize therapeutic benefits while minimizing side effects [33].
- Treatment Duration: The therapeutic effects of BoNT typically manifest within 6 weeks post-injection and can last for several months, necessitating periodic re-administration for sustained benefit [34].
- The ELATE trial is an ongoing study, investigating the efficacy and safety of onabotulinumtoxinA in patients with upper limb essential tremor. While focused on limb tremors, findings may have implications for head tremor treatments [35].

4. Conclusion: Over the past decades, botulinum neurotoxin (BoNT) has transitioned from a specialized neuromuscular blocker to a versatile therapeutic agent with vast applicability across neurology. Its expanding utility in motor, sensory, and autonomic disorders underscores both its clinical adaptability and favorable safety profile. Despite certain limitations—such as the necessity for repeated administrations and the rare occurrence of antibody formation—BoNT continues to gain prominence in neurologic therapies. Anticipated advancements, including the development of long-acting formulations, gene-based delivery systems, and individualized treatment protocols, hold promise for enhancing therapeutic precision and durability. Overall, the growing body of clinical evidence and ongoing innovation reinforce BoNT's integral role in modern neurology, offering targeted symptom relief with minimal systemic impact.

Authors' contribution

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